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Council assigned Nov '57
Action

PRIVILEGED COMMUNICATION
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
DIVISION OF RESEARCH GRANTS
Bethesda 14, Maryland

Rec'd 5-24-'57

Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

APPLICATION FOR RESEARCH GRANT

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C-3666

S.E.O.H. (1)

Former grant No. if different

Date May 20, 1957

Application is hereby made for a grant in the amount of $ 31,202.00 (omit cents) for the period from May (Month) 20, (Day) 1957 (Year) through May (Month) 19, (Day) 1958 (Year) inclusive for the purpose of conducting a research project on the following subject:

(LIMIT TITLE TO 53 LETTERS AND SPACES)

Title Of Project: Tumor Enhancing and Carcinogenic Effects of Air Pollutants Correlated with Human Cancer Epidemiology

Name, Title And Address Of Principal Investigator

Dr. Hardy A. Kemp, Chairman
Department of Public Health
Baylor University College of Medicine
Dr. Benjamin A. Rubin, Asst. Professor
Department of Preventive Medicine
Baylor University College of Medicine
Houston 25, Texas

Names And Titles Of Co-investigators, If Any

Dr. Arthur Kirschbaum, Chairman
Department of Anatomy
Mr. Alan C. Love, Chief Engineer
City of Houston Health Department
Dr. Thomas S. Osdene, Asst. Biochemist
Univ. of Texas M. D. Anderson Hospital
and Tumor Institute

Name Of Financial Officer To Whom Check Should Be Mailed

Alfus O. Johnson

Title And Address Of Financial Officer

Business Manager
Baylor University College of Medicine
Houston 25, Texas

Check Should Be Made Payable To:

Baylor University College of Medicine

Page 3 omitted—no entries. (RG)

AGREEMENT

It is understood and agreed by the applicant: (1) That funds granted as a result of this request are to be expended for the purposes set forth herein; (2) that the grant may be revoked in whole or part at any time by the Surgeon General of the Public Health Service, provided that a revocation shall not include any amount obligated previous to the effective date of the revocation if such obligations were made solely for the purposes set forth in this application; (3) that all reports of original investigations supported by any grant made as a result of this request shall acknowledge such support; (4) that, if any invention arises or is developed in the course of the work aided by any grant received as a result of this application, the applicant institution will either (a) refer to the Surgeon General for determination, or (b) determine in accordance with its own policies, and subject to the terms of its agreement with the Surgeon General dated _____, whether patent protection on such invention shall be sought and how the rights in the invention, including rights under any patent issued thereon, shall be disposed of and administered, in order to protect the public interest.

NAME OF INSTITUTION Baylor University College of Medicine

NAME AND TITLE OF OFFICIAL AUTHORIZED TO SIGN FOR INSTITUTION (Please Type) Stanley W. Olson, Dean

PERSONAL SIGNATURE (This agreement must carry the actual signature of the official whose name appears on the line above.) Stanley W Olson MD

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PHS-398
Rev. 2-56

PRIVILEGED COMMUNICATION

Form Approved
Budget Bureau No. 68-R249.5

Source: https://www.industrydocuments.ucsf.edu/docs/nqpl0000

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C-3666

PROPOSED BUDGET, for the period shown on page 1

NOTE: Under column entitled "OTHER" indicate funds presently available or anticipated from other sources including own institution.

	BUDGET	
	REQUESTED FROM P.H.S (omit cents)	OTHER
PERSONNEL (ITEMIZE ALL POSITIONS BY INDICATING TYPE; NAMES OF PROFESSIONAL PERSONNEL, IF SELECTED)		
Dr. B. A. Rubin	REDACTED	
Chemist		
Laboratory Assistant		
Animal Caretaker, half time		
PERMANENT EQUIPMENT (Itemize)		
High Velocity Equipment	1,000.00	
Gas Sampling Equipment	1,000.00	
Air Flow Measurement and Calibration Equipment	1,000.00	
Animal cages, 3 racks	1,500.00	
CONSUMABLE SUPPLIES (Itemize)		
Animals, feed, laboratory supplies, reagents, filters, etc.	3,000.00	
TRAVEL (State Purpose)		
Scientific Meetings and Consultations in other laboratories	1,000.00	
OTHER EXPENSE (Itemize) Transportation for sampling equipment	1,000.00	
Chemical consultations and Commercial analysis	3,000.00	
Equipment maintenance	500.00	
Social security and other	500.00	
SUBTOTAL (Direct Costs)	$ 27,150.00	
PHS PARTICIPATION IN INDIRECT COSTS (omit cents — adjust to low dollar)	4,052.00	
TOTAL BUDGET (omit cents)	$ 31,202.00	

NOTE: The administrative official signing this application may add an amount for indirect costs in accordance with the instructions.

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ESTIMATE OF FUTURE REQUIREMENTS—applies to funds needed from the Public Health Service for the years subsequent to the period proposed for this application. The spaces at the right are to be used to indicate the amount of support needed for each year, showing the direct and indirect costs as appropriate. DO NOT LEAVE ANY SPACES BLANK—if no additional support is required, enter "None". FOR FURTHER INFORMATION: See detailed instructions accompanying application form.

	DIRECT COSTS	INDIRECT COSTS	TOTAL
1	$27,150	$ 4,052	$ 31,202
2	27,150	4,052	31,202
3	27,150	4,052	31,202
4			

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Rev. 7-64

Source: https://www.industrydocuments.ucsf.edu/docs/nqpl0000

1. Research Plan

A. Specific Aims

To evaluate the carcinogen enhancement of tumor growth as a method for the determination of carcinogens in complex mixtures such as those derived from air sampling. To relate these determinations to other measures of air pollution and carcinogenicity. To compare effects so detected in local areas with the cancer epidemiology of those areas. To isolate and identify the fractions in air samples that are capable of producing this effect.

B. Method of Procedure

The solid content of measured volumes of air will be collected in a standard manner with the assistance of the Houston Department of Health in consultation with the Robert A. Taft Center of the U.S. Public Health Service. Mobile collection equipment will be situated in places where good cancer frequency data already exists and where further detailed studies are being made by the Cancer Epidemiologists of the Texas Medical Center. These areas will include the environs of several urban areas together with comparatively rural sections where no abnormal pollution is present. These will be selected on the basis of location, population stability, and completeness of medical recording.

Chemical and analytical treatment of these samples will be patterned after the methods developed in cooperation with the Taft Sanitary Engineering Center. Similar types of fractions obtained from them will be compared with our materials.

Our present biological technique consists in the skin painting of Dba/2 mice with suspected carcinogens dissolved in benzene or other appropriate solvents. Groups of at least six young (2-4 month old) mice are painted (0.1 ml of mixture applied) three times a week for a total of six weeks. One week after the last painting a suspension of tumor cells (Gardner Lymphosarcoma - 6C3HED) is injected subcutaneously into the axillae of treated and untreated mice. The tumor is carried in our inbred line of C3H mice and is prepared in a standard manner designed not only to avoid the destruction of the whole cells but to separate them well. The usual dose of 1 to 2 x 10^7 viable cells causes measurable growth by the fifth to sixth day. This either regresses within ten days or kills by progressive growth in 15-20 days.

In view of our being able to test small amounts of complex mixtures relatively rapidly, it is possible to further fractionate the mixtures beyond the present techniques of the Taft laboratory and thus to determine the active fractions. Identification of these fractions will be attempted with the help of such analytical facilities as infra red spectroscopy, mass spectroscopy, x-ray crystallography, and other methods available in nearby commercial laboratories.

Active fractions from different areas and situations will be compared and mixtures and fractions found effective in causing significant enhancement of tumor growth will be similarly painted on a group of 30 Dba/2 mice. This strain of mice has been repeatedly studied in this laboratory for spontaneous and carcinogenic development of neoplasms and the rates are well known and reproducible. These mice respond to known carcinogens within 18 months with greatly increased malignancy rates. Thus the induced cancer rate will be compared with controls and with the tumor enhancement phenomenon.

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C. Significance of this Research

Present methods of analysis for carcinogenic effect are slow. Moreover they require many animals and relatively large amounts of materials and time. The method we employ not only shows promise of correlating closely with classical methods of carcinogen detection. Thus we are in a position to fractionate complex mixtures found in air and put them to a sensitive test requiring only a small fraction of the test sample ordinarily needed. This could greatly speed up the identification of the offensive components of air pollution and perhaps help to identify the different carcinogens related to specific types of air pollution.

Although our assay is not one for carcinogenesis per se, this study which does compare it to classical methods may delineate the usefulness of this simple objective procedure.

The excellent cancer data collected in this area and state by the Texas Medical Center Epidemiology Services makes it possible to compare air studies to known clinical responses. In this way, carcinogenesis in mice as well as the tumor enhancing effect could be realistically evaluated in terms of actual human effects.

D. Facilities Available

We have available a colony of about 25,000 mice of some 15 inbred strains. Our group of Dba/2 mice susceptible to the carcinogen enhancement effect is large enough to immediately initiate large scale studies.

We have complete biological and chemical laboratory facilities with all of the usual equipment. Also available for coordinated study is some of the air sampling equipment of the City of Houston and the use of excellent commercial analytical facilities.

2. Previous Work Done on this Project

We have been studying the occurrence of spontaneous and carcinogen induced neoplasms in several strains of mice (including the Dba/2) for about three years.

About two years ago, in connection with experiments concerning the effect of tumor immunity on the incidence of carcinogen-induced tumors, we noted that in Dba/2 mice (and related Db strains) the 6C3HED lymphosarcoma grew progressively after methylcholanthrene treatment.

Subsequently we showed that a variety of known carcinogens as well as x-ray had this effect. As little as 30 micrograms of 9,10-dimethylbenzanthracene on the skin of each mouse was sufficient to cause progressive growth in 50 per cent of treated mice. Much smaller quantities measurably increased the size of the tumors. Related hydrocarbons that are non-carcinogenic were without effect.

This effect was not related to the expression of immune response to

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unrelated antigens (sheep or chicken erythrocytes) and was only very slightly affected by large doses of corticosteroids.

When mice susceptible to tumor growth enhancement with carcinogens are crossed with non-susceptible strains, all of the F1 progeny are non-susceptible. But 25% of F2's are able to respond. Thus we showed that this responce was governed by a recessive genetic mechanism that is quite different from the invariably dominant H2 system.

The City of Houston engineers have been collecting air contaminants for more than three years and are well acquainted with related techniques.

3. Personal Publications

Rubin, B.A., N. Ida and A. Kirschbaum 1956 Growth enhancement of a transplanted mouse lymphosarcoma. Proc. Cancer Res. 2:143.

Rubin, B. A. and A. Kirschbaum 1956 The effect of antibiotics on the growth of a transplanted lymphosarcoma in mice. Bact Proc. 1956:66.

Rubin, B. A. and N. Ida Studies on the mechanism of growth enhancement of transplanted mouse tumors by carcinogens. Proc. Cancer Res. 2:244.

Rubin, B. A. and E. B. Ward 1957 A new genetic factor affecting tumors transplantation in mice. Genetics. in press.

4. Results Obtained by Others

The carcinogenic nature of air contaminants has been demonstrated by Clemo, et al (1). Waller (2) has detected known carcinogens (3,4 benzpyrene) in numerous air samples. Much recent evidence showing the systemic effect of carcinogens is reviewed by Berenblum (3). The recent work of Baldwin (4) and of others indicates that carcinogens cause a decrease in the natural resistance of an animal to the growth of spontaneous tumors, which might otherwise be resisted. Other work by Malmgren, et al (5) and by others demonstrates further that changes in host susceptibility may be a significant facet of carcinogen activity.

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(1) Clema, G.R., et al. Carcinogenic Action of City Smoke. Brit. J. Cancer. 9:137 (1955).

(2) Waller, R.E. The Benzpyrene Component of Town Air. Brit. J. Cancer. 6:8 (1952).

(3) Berenblum, I. Carcinogenesis and Tumor Pathogenesis, in Advances in Cancer Research. Vol. 2, Academic Press, New York, 1954.

(4) Baldwin, R.W. Immunity to Methylcholanthrene-Induced Tumors in Inbred Rats following Atrophy and Regression of Implanted Tumors. Brit. J. Cancer Res. 9:652 (1955).

(5) Malmgren, R.A., et al. Reduced Antibody Titers in Mice Treated with Carcinogenic and Cancer Chemotherapeutic Agents. Proc. Soc. Exptl. Biol. & Med. 79:484 (1952).

Source: https://www.industrydocuments.ucsf.edu/docs/nqpl0000

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5. Biographical Sketches

Rubin, Benjamin Arnold. Ph.D. 1947, Yale University (Microbiology). Assistant Bacteriologist, U.S. War Department 1940-44; Research Microbiologist, Schenley Research Institute, 1944-45; Immunochemist, Yale University, 1945-47; Associate Microbiologist, Brookhaven National Laboratory, 1947-52; Chief Microbiologist, Syntex S.A., 1952-54; Research Associate, Department of Medicine, Baylor University College of Medicine, 1954; Asst. Professor of Preventive Medicine, Baylor University College of Medicine, 1955-present. Member.

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Kemp, Hardy Alfred. M.D. 1926, St. Louis University. Interne, William Beaumont Gen. Hosp. El Paso, Texas, 1926-1927; Assoc. Prof. Bacteriology and Hygiene, Baylor University, 1928-34; Prof. Bacteriology and Preventive Medicine, 1934-39; Dean, College of Medicine, and Professor of Preventive Medicine, University of Vermont, 1939-41; Dean, College of Medicine, and Director of University Hospital, Ohio State University, 1941-44; On military leave, 1942-45; Dean, College of Medicine, and Professor of Preventive Medicine, Wayne University (Detroit), 1945-48; Professor of Preventive Medicine and Chairman, Dept. of Public Health and Preventive Medicine, Director of Graduate Studies, Baylor University College of Medicine, 1948-present; Div. Medical Consultant (Industry) Liberty Mutual Insurance Company, 1950-present.

Kirschbaum, Arthur. Ph.D. 1936; M.D. 1943, Minnesota. Alexander Brown Coxe Fellow, Finney-Howell Fellow, Instructor in Anatomy, Yale, 1937-41; Instructor, Assistant Professor, Associate Professor Anatomy, Minnesota, 1941-51; Professor and Head of Anatomy, Illinois, 1951-54; Professor and Chairman, Anatomy, Baylor University College of Medicine and University of Texas Dental Branch, Consultant M.D. Anderson Hospital and Tumor Institute, University of Texas, 1954-present. Societies:

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Consultant, Public Health Service (Morphology and Genetics Study Section), 1951-present.

Love, Alan C. B.S. 1932, Texas A. & M (Sanitary Engineering): M.S. 1938, Harvard Univ., (Sanitary Engineering). Public Health Engineer, City of Houston, Reg. Professional Engineer; Austin-Travis County Health Unit, 1938-42; Public Health Engineer Waco-McClennan County Health Unit, 1942-45; Private Engineering Operations, 1945-51; Chief Engineer, City of Houston, Department of Health, 1951-present. Reserve Commission Public Health Service, 1941-45. Fellow Public Health Assn.;

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Osdene, Thomas S. B.Sc. 1951 (1st class honors), University of London; Ph.D. 1955 (Organic chemistry), University of London. College Chemistry Prize, Birbeck College, University of London. Research Chemist, Chester Beatty Research Institute, London, 1951-55; Research Assistant, Princeton University, 1955-56; Assistant Biochemist, University of Texas, M. D. Anderson Hospital and Tumor Institute, September 1956-present. Societies:

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